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Canine hyperthermia with cerebral protection

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Canine hyperthermia with cerebral protection

by

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LIST OF SYMBOLS

D=t Died=time after treatment (hrs.)

E Euthanized in one week

f Respiratory rate (min^{-1})

t Time (min)

T Temperature, °C

Subscripts:

B Bath

B_r Brain

c Core

f Respiratory rate (min^{-1})

i Initial

N Irrigation (Nose)

sc Subcutaneous

INTRODUCTION

The febrile response is commonly believed to be an attempt of the host to create an unfavorable environment for the growth and reproduction of a pathogen (11). This aids other defense mechanisms of the host in the suppression and destruction of invading organisms.

Much effort has been expended toward understanding thermoregulation and the febrile reaction (1,34). Hypothermia has been used to lower the metabolic rate of human and animal patients to prolong time-critical surgical procedures. Hyperthermia has been studied in an effort to determine how the homeothermic animal is able to maintain its thermal set-point. Regional hyperthermia has long been used to aid in the localization of inflammatory processes in the animal appendage. Blood supply to the area is increased, metabolic rate of the host cells is increased, and the elevated temperature creates an unfavorable environment for the growth of pathogenic organisms. If regional hyperthermia could be extended to whole body hyperthermia, a simple, non-invasive, safe technique could be added to the techniques presently used to combat certain illnesses.

Each organ system, which comprises a specialized group of cells for performance of a specific function or group of functions, may be characterized by its metabolic rate and its ability for self-repair (2,13). Each organ system may also be

characterized by its heat producing capacity, which is determined by its metabolic rate and the type of chemical reaction occurring. Each organ system has a maximum thermal tolerance level (42,43,44,71,75).

The maximum thermal tolerance level of the whole organism is limited by the organ system most susceptible to heat, by the ability of that system to repair nominal thermal damage and by how essential that system is to the life of the animal.

In vitro and in vivo studies indicate the central nervous system is the organ system most susceptible to heat. Evidence indicates the brain is one of the most heat-sensitive organ systems of the body (8,9,71). The cerebral cortex is especially sensitive, due to its extremely high synaptic metabolic rate, high oxygen requirements and poor ability to repair nominal damage. If the cerebral cortex could be thermally protected, the core temperature could be elevated to the maximum thermal tolerance level of the next most sensitive system.

The temperature of the cerebral cortex and the diencephalon can be influenced by nasal irrigation (51,52,53, 54). It should therefore be possible to temper an extreme core temperature to render it compatible with the cerebral cortex. This work was initiated in an attempt to find the maximum thermal tolerance level of the canine when the cerebral cortex is selectively protected by nasal irrigation.

LITERATURE REVIEW

Thermoregulation

Two thermoregulatory centers have been identified within the central nervous system (12,57). Located in the medial preoptic area is the paired heat loss center. The other center is called the heat production and conservation center. This paired center is located in the caudal hypothalamus dorsolateral to the mammillary bodies (6,7,12). Stimulation of the heat loss center in the canine induces cutaneous vasodilitation, panting, salivation, and decreased muscle tone. The heat loss center also has an influence on the supra-optic and paraventricular nuclei so that during excessive salivation or sweating the antidiuretic hormone is released, conserving body fluids by renal water retention (4,5,6,7,12). Stimulation of the heat production and conservation center causes vasoconstriction of cutaneous vessels, pilierection, increased secretion of epinephrine, and shivering (5,12,30,37). Inhibitory information passes between the heat loss center and the heat production center. This functions as a servomechanism to aid in regulation of the thermal set point (12,38,49,50). These centers receive information about the thermal state of the external environment. This information is sensed by thermoreceptors located in the skin (49), transmitted by afferent nerve fibers to the central nervous system, and passed up the

lateral funiculus of the spinal cord to the hypothalamus. Thermoreceptors are also located around the thermoregulatory centers in the brain. They function to sense the blood temperature of the hypothalamus (12,59).

Thermoreceptors are also located somewhere in the core tissues of the body (32). Thermal information from all sources is received by the thalamus, and is relayed to the thermoregulatory centers, as well as to other parts of the brain. The thermoregulatory centers integrate all the sensory inputs with the other body functions to maintain the thermal set-point.

Information calling for conservation of heat or heat dissipation is distributed to various parts of the brain from the thermoregulatory centers. The thermoregulatory center thus has been considered a body thermostat (34). The thermal operating point or set-point has been studied quite extensively. Hardy (34) summarized the results of many investigations by stating that temperature is the regulated variable, and that the regulator has the properties of proportional and rate control, but not integral control. Guieu and Hardy (30) found that the preoptic area functioned as an area of integration as well as initiation of temperature information. Transient and long-term thermal stresses affect thermal receptors differently. Thermal stress originating from inside the body also affects the thermal receptors differently from those originating from

outside (34).

The regulation of body temperature in the cold or neutral zones is largely affected by the peripheral receptors, whereas regulation of body temperature in the hot zone is more under the control of the central receptors (34).

The three important effector elements of thermoregulatory control are the metabolic response to cold, the sweating or panting response to heat and control of the vasomotor exchange. Below environmental temperatures near neutrality the vasomotor system is in a full state of constriction. This results in a minimum of heat flow from the blood to the surface. Above the environmental temperature zone near neutrality (28-30°C) there is reduction of vasomotor tone and active vasodilator activity (17,18,28), causing a marked increase in peripheral conduction. In the zone of vasomotor regulation, minor increases and decreases in tissue conductance maintain thermal balance.

The tongue of the dog is an important blood-air heat exchanger during hyperthermia, as was pointed out by Ederstrom (16). He observed large increases in flow to the tongue, with little increase to the foot, ear or intestine. The skin is not an important mechanism of heat dissipation in the dog, as evidenced by the sparsity of sweat glands (58).

Murakami et al. (59) found a diminished response to temperature change following the administration of anesthesia. Of the anesthetics he studied, chlorolose-urethan was the least

depressive. Ingram and Smith (41) found that some anesthetics produced persistent vasodilation, but with methoxyflurane and urethan their results indicated a curvilinear relationship between brain temperature and peripheral blood flow over the entire range of brain temperatures. They concluded the effects of direction and rate of change of brain temperature were equivocal. Type of anesthetic and the level of its use also influences the heart rate and electrical activity, and the respiratory rate and depth. Methoxyflurane, used at light anesthetic levels, has little influence on these activities but will put the animal in a mild state of metabolic acidosis (67).

Influence of Temperature on Metabolism

Chemical reaction rates of body metabolism roughly follow van't Hoff's rule, which states that the velocity of chemical reactions is increased two-fold or more for each rise of 10° centigrade in temperature. Dukes (72) restricts this to more physiological limits by stating that a rise of 1°C causes an increase of 10 to 20% in metabolic rate. In man, a 13% elevation in metabolic rate for each degree centigrade is seen. Hubbard et al. (40) describes the Q_{10} as the ratio between the metabolic rate at a given temperature and the rate at a temperature 10°C higher. Therefore, when the Q_{10} is measured, the temperature range must also be given. Comparisons are relevant only when temperature ranges are exactly the same.

They are, thus, not really linear over a wide biological range.

Whole body hypothermia was used in 1938, when body temperature was reduced to 32.2°C. Later, temperatures were reduced to 27.5°C and 21.1°C. Hypothermia aided in reducing the metabolic rate of the patient, thus affording an increase in time available for surgery (20,48). It was also used in attempts to reduce edema in cases of severe human cerebral trauma (21). Local hypothermia was accomplished by circulating ice water through a capsule inserted into the skull, but was accompanied by brain abscesses and cerebritis. There was bradycardia, depressed respiration and increase in pulse pressure. Cerebral hypoxia and ventricular fibrillation are complications of whole body hypothermia (20).

When the environmental temperature is increased such that cooling by convection and radiation cannot eliminate metabolic heat, panting or sweating is initiated and the excess heat is released by evaporation (72). The threshold for increased evaporative heat loss is influenced by time and temperature of exposure, acclimatization, health of subject and level of basal metabolic rate (33,46,55,56). Heart rate is also increased, and urine production is diminished (26,36,43). In the dog, Hammel et al. (33), have noted a linear relationship between rectal temperature and panting on exposure to heat. With an increase in rectal temperature from 38 to 38.8°C, there is a twenty-fold increase in evaporative heat loss from the lungs.

Findley (24,25) noted that as respiration rate increased, actual pulmonary ventilation remained almost constant. Panting results in evaporative cooling in the upper respiratory passages and does not cause cooling in the lungs (24,65). After a period of panting, pCO_2 decreases, pH increases and blood lactate is elevated (17,26,42,68). Urinary output drops, due to a decrease in renal plasma flow (42,43,62). Plasma cortisol levels increase (14) and cardiac output is increased (63).

Durotoye and Grayson (15) studied production of heat in the gastrointestinal tract of the dog. They found the duodenum was 0.6°C hotter, and the ileum, stomach and large intestine were 0.5°C hotter than the aorta. The portal vein was 0.35°C hotter than the aorta, while the rectum had the same temperature as the aorta. They concluded that the G. I. tract produced 60% more heat than the liver, and that splanchnic heat accounted for about 33% of the total body heat production.

In animals that pant (dog, sheep, swine), the thermal stimuli for panting arise primarily from core receptors and peripheral receptors (32,74) and these stimuli will override the chemoreceptor center for respiration if the animal becomes alkalotic (31).

Alterations in tissue electroyte concentrations indicate changes in membrane permeability. Spurr and Barlow (68) noted that if the canine rectal temperature were elevated to 42.5°C for one hour, electrolyte and fluid shifts occurred in various

body tissues. He noted an increase in intracellular sodium in the liver, jejunum and brain, and a decrease in intra-cellular potassium in the liver and jejunum. He concluded these organs contributed heavily to extracellular potassium concentration.

Other dyscrasias become evident during the extreme hyperthermia. Field et al. (23) found a disappearance of reflexes and death at 42-45°C in the rat. He concluded that this was the temperature range where a progressive decrease in O_2 consumption occurred. In the pig, maximum respiratory rate was recorded at rectal temperatures of 41 to 41.5°C. If rectal temperature exceeded 41.5°C, respiratory rate declined and death was imminent (69). In a study of human patients that suffered heat stroke from a mining accident, 90% survived. These patients suffered centrolobular degeneration or necrosis of hepatocytes and congestion. These changes were completely reversible and were believed to be due to hypoxia and thermal injury (44).

Frankel et al. (26,27) intensively studied blood chemistry during progressive hyperthermia. Changes in blood chemistry began to develop at the critical temperature of 42°C. Studies of blood gases and lactates demonstrated that tissue hypoxia developed. He concluded that failure of external respiration was not the primary physiological derangement during progressive hyperthermia. In studying liver lactates, pyruvates and

pyridine nucleotides, Frascella and Frankel (28) concluded that the site of initial failure during progressive hyperthermia was not the mammalian liver.

Burger and Fuhrman (13), utilizing in vitro studies, found the cerebral cortex more sensitive to heat damage than the liver or the renal cortex. His technique utilized decrease in O_2 consumption as the biochemical criterion. He found damage to the cerebral cortex after sixty to ninety minutes, with the temperature held at 40-41°C, and also after thirty to forty minutes at a temperature of 43°C. The liver was damaged by temperatures of 45°C for sixty minutes, the demonstrable kidney damage required 44°C for sixty minutes.

Nemoto and Frankel (61) felt that cerebral failure was not due to cerebral hypoxia, but to limitation of the nucleotide supply required for cerebral glucose transport. During his series of investigations of progressive hyperthermia, elevation of cerebral O_2 consumption and glucose consumption was reversed between 42°C and 43°C. Upon examination of Purkinji cells from rats which were stressed at 40 to 42°C for three hours, Kucherenko (46) noted reactive and destructive changes of cellular membrane systems. Swelling of mitochondria, clearing of the mitochondrial matrix, and partial destruction of the cristae were observed. Fragmentation of membranes of the endocytoplasmic reticulum and Golgi hypertrophy were also seen. Lysis of the degenerative products occurred in six hours, with restoration of normal ultrastructure in twenty-four hours.

Studying independently, Wang et al. (75) and Rozanora et al. (64) felt that uncoupling of oxidative phosphorylation may be a mechanism of cellular breakdown during acute hyperthermia. Denaturation of proteins, especially of enzyme systems, was also observed in cerebral tissue during hyperthermia (2,70,71,73).

In examining the above information, the CNS is implicated as the first organ system to succumb to extreme hyperthermia. Evidence also incriminates the denaturation of enzymes and/or an uncoupling of oxidative phosphorylation as the mechanism of action.

Fever

Fever is an elevation of body temperature in response to some diseases. It is a mechanism whereby the body creates an unfavorable environment for a disease condition (11). Perfusion of the cerebral ventricles with sodium ions markedly increases the body temperature, while perfusion of calcium ions decreases body temperature (22,60). Possibly, the thermal set-point may be raised by altering the balance between these two actions in the cerebrospinal fluid (60). However, most investigators agree with Atkins (11) that the mechanism of action involves the release of bacterial endotoxins. Bacteria release an endotoxin which, in turn, causes granulocytes to release an endopyrogen. This endopyrogen acts on the thermoregulatory center to cause an elevation in body temperature.

Atkins also stated that a disease process becomes less severe if the body temperature is raised artificially, thereby adding credence to the concept that fever is a defense mechanism.

Von Ardenne et al. (8,9,10) was able to arrest growth of several types of carcinogenic tissues in rats and mice by exposing them to hot water baths of varying temperatures for appropriate durations. After treatment at 40°C for one hour, two hours, or four hours, the experimental animals, as well as the control animals, had mitotic figures in the cancerous tissue. At 41°C for sixty minutes, animal death occurred because of the excessive heat. But at 40.5°C for sixty minutes, tumor growth in heat-treated rodents was arrested for a period of two to six months, while untreated rodents died within a two-week period. Von Ardenne improved his results by combining hyperthermia with the use of cyclophosphamide, a chemical used as an aid in arresting certain types of carcinogenic proliferation. He postulated that hyperthermia caused denaturation of the enzyme systems in cancerous tissue before it affected the normal tissue. It also increased membrane permeability, thereby permitting an increased amount of cyclophosphamide to enter the cells. Kirsch et al. (45) confirmed the latter statement with P_{32} labeled cyclophosphamide.

Cerebral Heat Exchange Mechanism

Magilton and Swift described a mechanism by which nasally respired air could influence the temperature of the brain (51, 54). This involved essentially two heat exchangers. One was the air-venous blood interface which was located at the alar fold of the nasal maxilloturbinate. This effectively cooled blood which drained to the second heat exchanger, which was a venous blood-arterial blood heat exchanger. The cooled venous blood received thermal energy from arterial blood that supplied the brain (52). Subsequent study revealed that this system was not passive. It was under dynamic vascular and neural control and through changes in temperatures exposed to the nasal mucosa a definite, repeatable alteration could be noted in temperature of brain parenchyma, cerebrospinal fluid pressure, blood pressure and heart rate (51,53).

Magilton and Swift (52,54) demonstrated by cold water irrigation that brain temperature could be decreased to 12°C below body temperature, although hot water irrigation could not elevate brain temperature much above normal body temperature.

Anatomy

The alar fold is a bilateral bulbous rostral extension of the maxilloturbinate in the dog. It is richly supplied with blood and contains large venous sinuses (58). The alar fold functions with the turbinates as a heat exchanger between the

blood and respired air (52).

The cooled venous blood draining the alar fold returns to the body by two separate routes after it is collected by the dorsal and lateral nasal vein. One is directly to the heart by the facial vein and the other is an indirect route which involves another heat exchanger. The latter route courses the blood through the angularis oculi vein over the ventro-medial angle of the bony orbit into the orbital canal, and continues through the ophthalmic vein, multifurcating into a venous plexus. The majority of the blood then enters the cavernous sinus, while a minor portion flows to the internal maxillary vein to return to the central venous pool (58).

The cavernous sinus is a cavity formed by the separation of the dural sheath of the brain, which is filled with venous blood. This sinus is constantly located on the floor of the middle cranial fossa. It is paired and connected anteriorly with the orbital plexus through the orbital foramen. The paired cavernous sinuses are connected medially by inter-cavernous sinuses rostral to and caudal to the stalk of the dorsum sellae. The hypophysis is located rostral to the rostral intercavernous sinus. A third intercavernous sinus may inconstantly be located rostral to the hypophysis (58). The intercavernous sinuses are small, which restricts the venous communication between right and left cavernous sinuses (51).

Laterally, emissary veins drain the cavernous sinus into the internal maxillary vein. The cavernous sinuses are continuous caudally with the ventral petrosal sinus, and the venous blood is returned to the central venous system through the internal maxillary vein or the vertebral venous sinuses (58).

The main arterial blood supply to the telencephalon (cerebral hemispheres) and the diencephalon (thalamus and hypothalamus) is via the internal carotid artery. The internal carotid artery enters the caudal carotid foramen through the petrobasilar fissure and traverses the carotid canal. It leaves the internal carotid foramen, passes ventrally through the external carotid foramen, forms a loop, and re-enters the external carotid foramen. It runs anterio-dorsally toward the dorsum sellae, then perforates one layer of the dura (58). The internal carotid artery is thus within the cavernous sinus. An anastomotic branch from the middle meningeal and orbital arteries forms a simple rete with the internal carotid artery (35). It courses for approximately three-quarters of an inch in the sinus before perforating the second layer of the dura and arachnoid. The internal carotid artery then trifurcates into the middle cerebral artery, the anterior cerebral artery and the posterior communicating artery (58).

Functionally, the internal carotid artery furnishes the blood supply to the central nervous system caudally to the

region of the rostral colliculus. This blood is then drained into the various dural sinuses of the cranial vault, and is returned to the central venous pool (58).

If the venous blood of the alar fold were cooled, the base of the brain would be cooled two ways, directly and indirectly. The first way is by direct extension through the dural surface from the cavernous sinus to the ventral portions of the brain. The second is by cooling the arterial blood supply to the cerebral hemispheres (52).

MATERIALS AND METHODS

In order to determine the maximum thermal tolerance level of a body system, core temperature must be controlled. Core temperature is a function of the thermal "set point" of the hypothalamus, temperature of the environment and temperature of respired air. It is readily apparent that only an indirect control of core temperature can be maintained.

Environmental temperature can be controlled most constantly by a circulating water bath. Length of hair, although maintained short in this series of experiments, does not interfere significantly with heat transfer into the skin from the water bath (39). This is because virtually all the heat transfer is through convection.

The warm water bath consisted of a hundred-gallon water tank mounted on wheels for maneuverability. Heat loss from the tank walls was minimized by attaching a one-inch-thick expanded foam plastic sheet to the outside.

The time required to cool the bath from 42°C to 41°C at room temperature was one hour. Water circulation was adequately maintained with a large submersible impeller pump.[1] No temperature gradients were observed in various locations in the tank when the temperature was held constant. Upon heating or cooling, the water transient gradients were noted, but no

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[1]Model no 7114, Cole-Parmer Instrument Co., Chicago, Ill.

thermal oscillations occurred because whirlpool effects were minimized.

Temperature of the water was increased or decreased by adding hot water (55°C) or cold water (10°C). Excess water was removed with another impeller pump.[1] The desired water temperature was quite easily achieved and maintained within narrow tolerance limits.

A restraining device made of rods was suspended in one end of the tank. The lower jaw was anchored to this device to immobilize the canine head. Care was maintained to not interfere with the venous drainage of the tributaries of the maxillary vein. This was the only restraint required to stabilize the partially submerged animal with the exception of anchoring the tail to prevent lateral deviation. Cold water nasal irrigating tubes were fabricated from a blood transfusion set. A hypodermic thermistor[2] was placed in the irrigating line within two inches of the outflow. Irrigating water temperature was held at approximately 8°C, $\pm$2°C, by a refrigerator coil. This water was circulated through the irrigation tubing to the nose by a roller pump[3]. Approximately symmetrical water pressure

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[1]Model no. 7111, Cole-Parmer Instrument Co., Chicago, Ill.

[2]Yellow Springs Instrument Co., Yellow Springs, Ohio.

[3]Randolph Pump model 500, The Randolph Co., Houston, Tex.

was maintained to irrigate only the alar fold of each nostril with the water returning cranially out of the nose. The water then fell into a pan and returned to the refrigerator reservoir. Endotracheal intubation, which was utilized for gas anesthesia[1], prevented any entrance of water into the trachea. It also prevented the tongue from functioning as a cooling organ.

Low resistance wire, with a steel needle electrode, was utilized for each of the three electrocardiographic electrodes. Modification of these leads was necessary to record heart electrical activity of the submerged dog. An epoxy film was placed over the lead to within three-eights inch of the tip. It was thus possible to place the electrode well under the skin of the animal and avoid any direct electrical contact between the water bath and the electrode. The high skin and epoxy resistance formed an effective shield from the water bath.

Three wheatstone bridge thermometers[2] with accompanying rectal probes were utilized to monitor two rectal temperatures and one bath temperature. Four thermistor needle electrodes[2] were each utilized in a resistive bridge circuit to monitor subcutaneous temperature. All thermistors were calibrated utilizing the same glass mercury thermometer as a reference. Equivalent resistances at 2°C increments were determined for

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[1]Metofane, Pitman-Moore, Inc., Ft. Wash., Pa.

[2]Yellow Springs Instrument Co., Yellow Springs, Ohio.

the needle electrodes. Calibrations were made before and after each experimental procedure.

Respiratory rate was measured by a thermistor placed in the endotracheal tube. Respiratory and heart rate, four subcutaneous temperatures, bath, nasal irrigation and rectal temperatures were continuously monitored on a twelve-channel pen recorder[1].

A schematic diagram (Figure 1) depicts the indirect control of core temperature by the manipulation of bath water and irrigating water temperatures.

Healthy mature pound dogs of either sex, that weighed between five and fourteen Kgms., were utilized for the experiment. Dog size was restricted by the water bath dimensions. During the two-week acclimatization period, baseline data were obtained. Baseline data consisted of a fecal examination for endoparasites, blood analysis, electroencephalogram[2], electrocardiogram[2], complete physical and neurological examination.

Blood analysis included determinations of packed cell volume, hemoglobin, total red cell count[3], total white cell count[3], differential white count, platelets, cell morphology,

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[1]Polygraph Model 7, Grass Instrument Co., Quincy, Mass.

[2]Dymograph Model R-411, Beckman Instruments, Inc., Schiller Park, Ill.

[3]Coulter Counter Model F$_n$, Coulter Electronics, Inc., Hialeah, Fla.

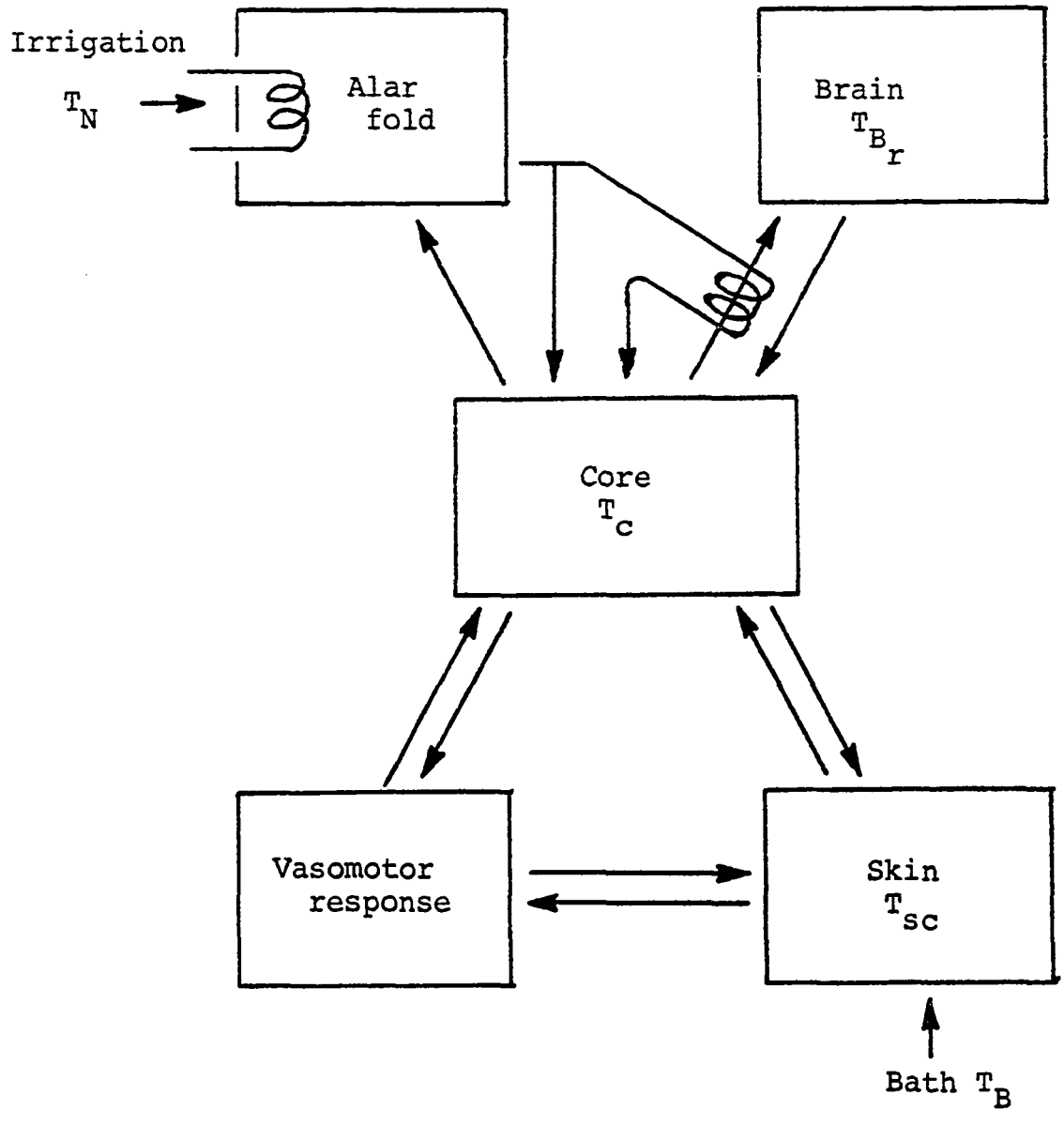

Figure 1. A schematic diagram depicting indirect control of T_c by manipulation of T_B and T_N

total protein[1], fibrinogen[1], blood urea nitrogen[2], serum glutamic pyruvic transaminase[3], sodium[4] and potassium[4] content. Animals that did not have acceptable "normal" values were eliminated from the experiment.

Feed and water were withheld eighteen hours prior to the experiment. Baseline data were obtained after animals were anesthetized prior to the experimental procedure. These data included another blood analysis, clotting time, urinalysis[5] and blood-gas[6] analysis. The urinalysis included qualitative determinations for blood, protein, sugar, pH and a microscopic examination. The blood-gas determinations involved partial pressure of oxygen (PvO_2), partial pressure of carbon dioxide ($PvCO_2$) and concentration of hydrogen ions (pH). Blood-gas measurements were again determined at a point two-thirds through the experiment. Immediately after the experiment, blood analysis, clotting time, blood-gas analysis, urinalysis (including specific gravity) and urine volume were again determined on the surviving dogs.

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[1]T. S. meter, American Optical.

[2]Unimeter model D-250, Biodynamics Inc., Indianapolis, Ind.

[3]Reitman-Frankel Procedure, Dade, Miami, Fla.

[4]Flame Photometer, Instrumentation Lab., Inc., Lexington, Mass.

[5]Hemacombistix Ames Co., Elkhart, Ind.

[6]Corning Model 16 blood gas analyzer, Corning Glass works, Corning, N.Y.

Surviving dogs were maintained without therapy other than nursing care for one week. At the end of that time, a blood analysis, ECG, EEG, neurological and physical examination were made prior to euthanasia. A necropsy was performed with tissue samples obtained for histopathological studies from the liver, spleen, kidney, pancreas, thyroid, thymus, parathyroid, lymph node, left ventricle, aortic valve, aorta, lung, urinary bladder, stomach fundus, descending duodenum, gall bladder, terminal ileum, diaphragm, skeletal muscle and sometimes the skin. Sections of the central nervous system included cerebral and cerebellar cortex, basal ganglia of the cerebrum and cerebellum, thalamus, septal area, hypothalamus, regions through the oculomotor and trochlear nucleus, brachium pontis, caudal medulla, and high cervical region.

Anesthesia was induced on two dogs with thiamylal Na.[1] After baseline samples were obtained, the dogs were placed in the 37° water bath side by side, but were spaced for maximum water circulation over the body surface.

Anesthesia was maintained in a light plane with methoxyflurane gas[2]. Heart rate and condition were monitored via lead II electrocardiogram.

Subcutaneous temperatures were obtained from the right and left mid-thoracic regions of both dogs. The electrode for

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[1]Surital, Parke Davis & Co., Detroit, Mich.

[2]Metofane, Pitman Moore, Inc., Ft. Wash., Pa.

recording rectal temperature was placed high into the colon, as close to the left colic flexure as possible.

Bath water was heated at the rate of one-half degree centigrade per minute until the desired bath temperature was reached. The two dogs were treated identically with the exception that when the core temperature of the dog to be irrigated reached 41°C, irrigation of the alar fold was initiated, with a water temperature of approximately 8°C. When the bath water reached the predetermined temperature, this temperature was maintained for a certain predefined period, the bath was then cooled back to 36°C at a rate of 1 to 2°C per minute. Fast recordings were obtained prior to bath heating and at ten-minute intervals throughout the procedure.

Bath temperatures of 41°C, 43°C, and 45°C were selected with each temperature held for durations of thirty, sixty and ninety minutes. Three pairs of dogs were included at each component of the time-temperature matrix, with the exception of each extreme, namely 41°C for thirty minutes and sixty minutes and the control component at 45°C for sixty and ninety minutes (Table 1).

Parameters to formulate the matrix were set to include time and temperature extremes of *in vivo* and *in vitro* studies (8,23,69,70). After initial trials the thirty and sixty minute blocks at 43°C were eliminated because a response of rapid respirations could not be elicited in the control dogs. At

45°C the control animals could not survive past fifteen to twenty-five minutes. The irrigated dogs exposed to 45°C for longer than one hour suffered such marked respiratory, cardiac and cutaneous alterations that this extreme was also eliminated.

Additional information was obtained by adding an irrigated group at 44°C and a control group at 42°C (Table 2). The core temperatures of these two groups were approximately the same. Core temperature along with bath temperature could therefore be held constant by comparing the various time-temperature groups with each other. Data were accumulated to formulate a descriptive mathematical model (66).

These additional experiments were conducted on only one dog at a time. Rectal and stomach temperatures were simultaneously recorded with subcutaneous temperatures of the right and left lateral aspect of the foreleg and the right and left lateral aspect of the rib cage next to the twelfth rib. Respiratory and heart rates were also monitored.

Brain temperatures of seven irrigated and three control dogs were compared to their own core temperatures. The brain thermistor probe was positioned in the right corpus striatum in a plane with the caudal aspect of the thalamus. The location was verified on post mortem examination.

The stomach and rectal temperatures of fifteen dogs were compared.

Table 1. Time-temperature matrix utilized with T_B held constant

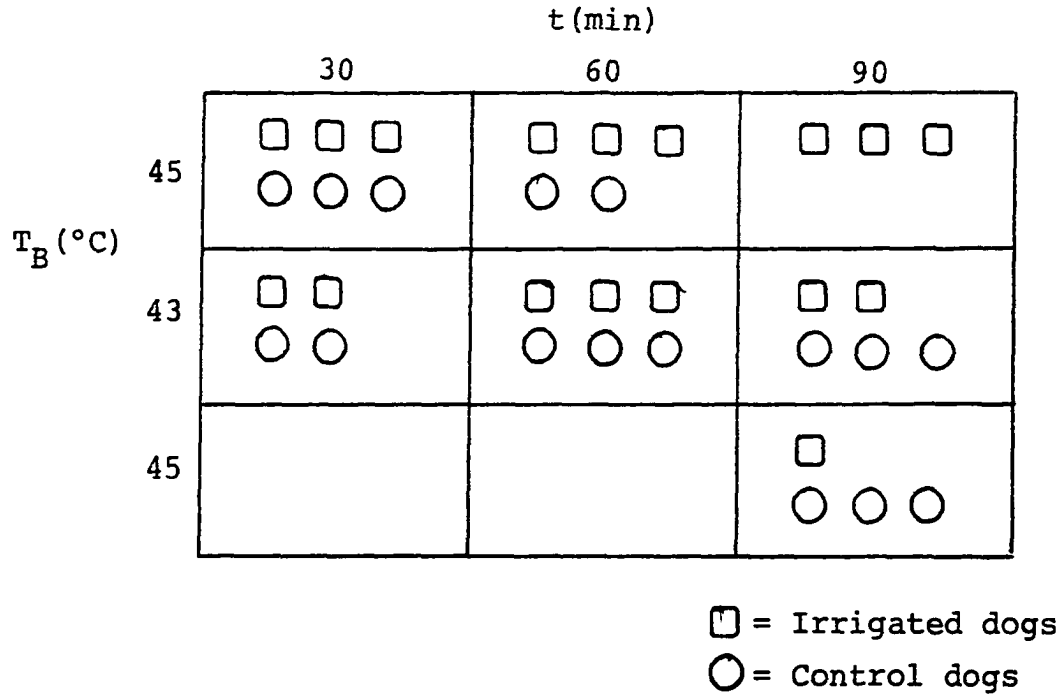
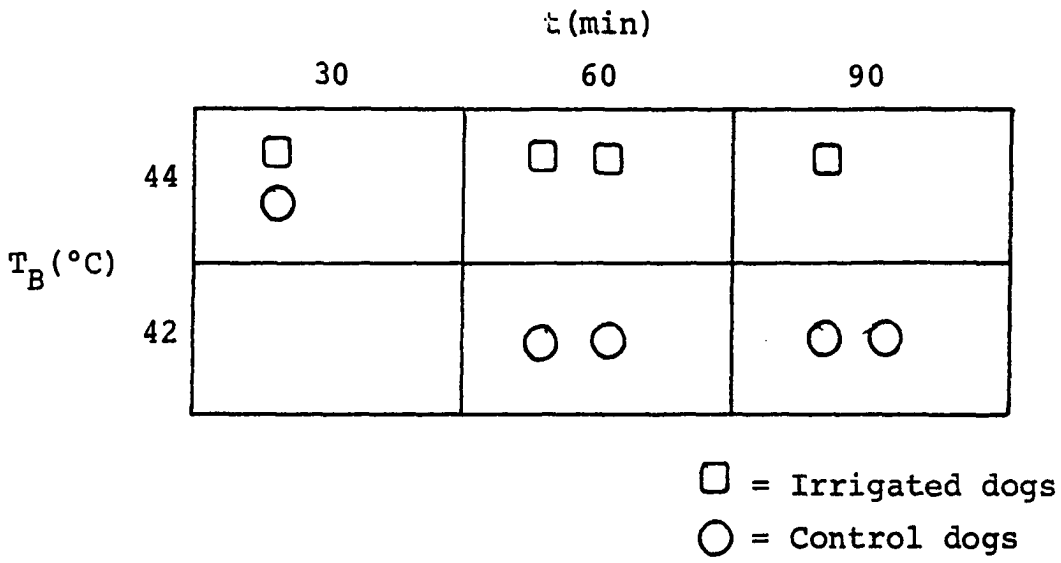


Table 2. Additional time-temperature matrix utilized with T_B held constant



RESULTS AND DISCUSSION

Temperature Responses

Maximum core temperatures of 42°C could be maintained for sixty to ninety minutes in non-irrigated dogs without termination in death. If core temperatures were elevated to 42.5°C for twenty minutes or longer, death occurred within twelve hours. If the animals were nasally irrigated, core temperature values could safely be elevated at least 0.5°C above the maximum for control animals, and the time duration could be extended as well. A summary of the thermal experimental data may be seen on page 65 of the Appendix.

A two degree elevation in bath temperature of an irrigated dog results in a core temperature comparable to that of a control dog. Figure 2 compares two dogs with similar core temperatures. Physiological responses of these two groups of dogs were compared, and it was determined that the thermal death point of non-irrigated dogs was reached after T_c = 42.5°C in excess of ten minutes, while that of irrigated dogs was reached after T_c = 43°C in excess of thirty minutes.

Respiration and character of the ECG were closely watched, and discrepancies in their patterns were consistent with proximity to death.

Tables 3 and 4 summarize the live-dead responses of animals at various time-temperature combinations.

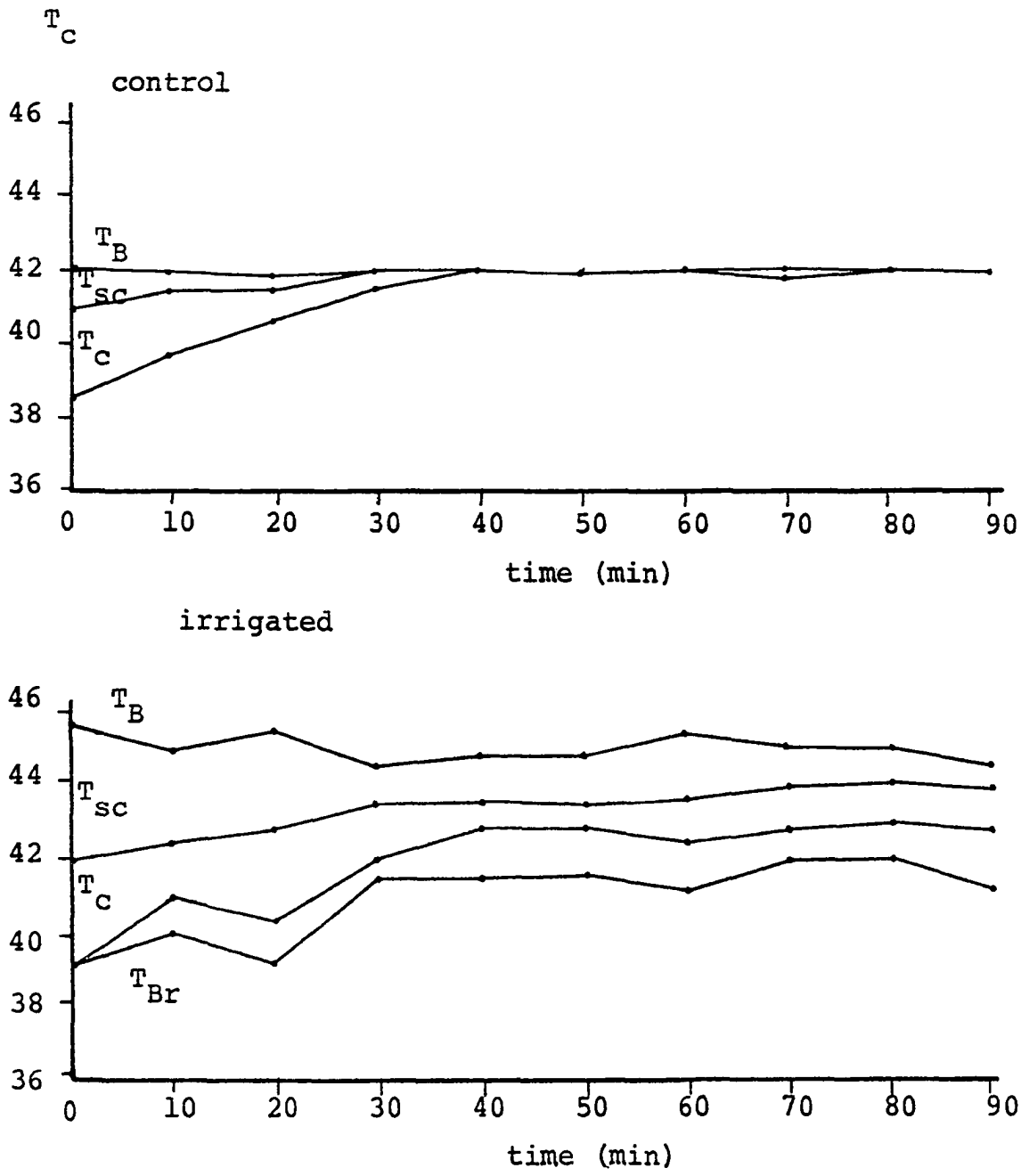


Figure 2. Comparison of irrigated and control dogs of similar core temperatures

Table 3. Time-temperature matrix depicting survival response to hyperthermia with T_B held constant

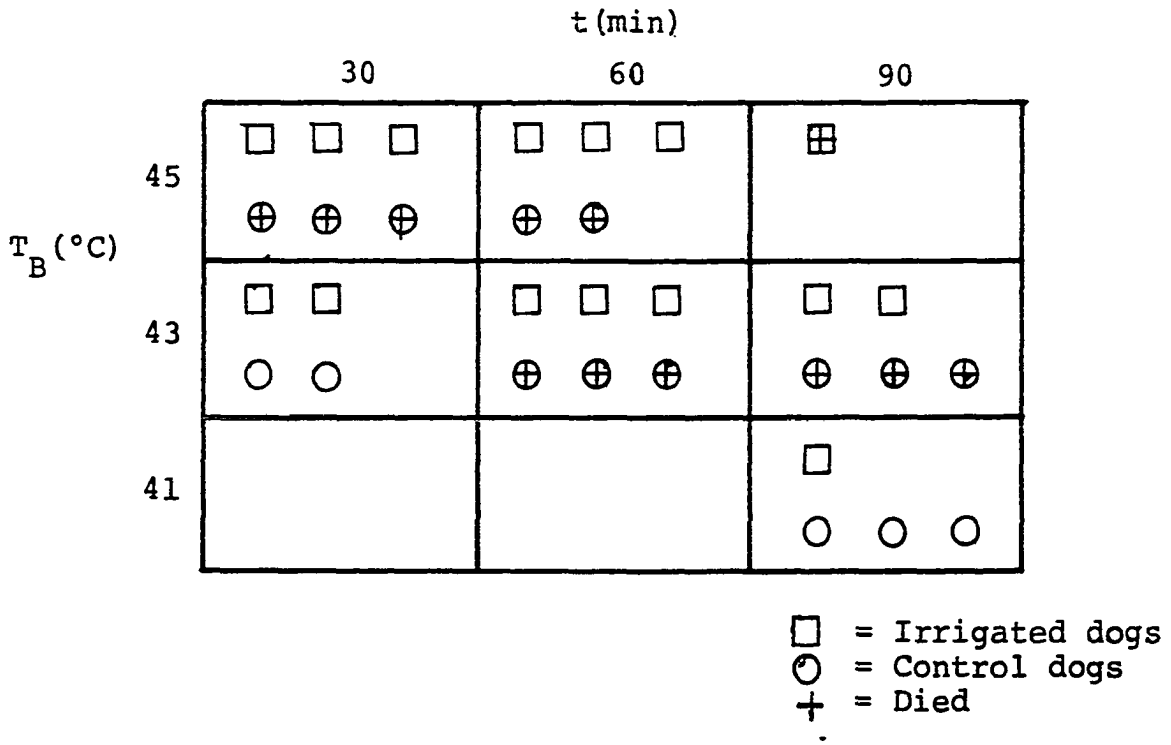
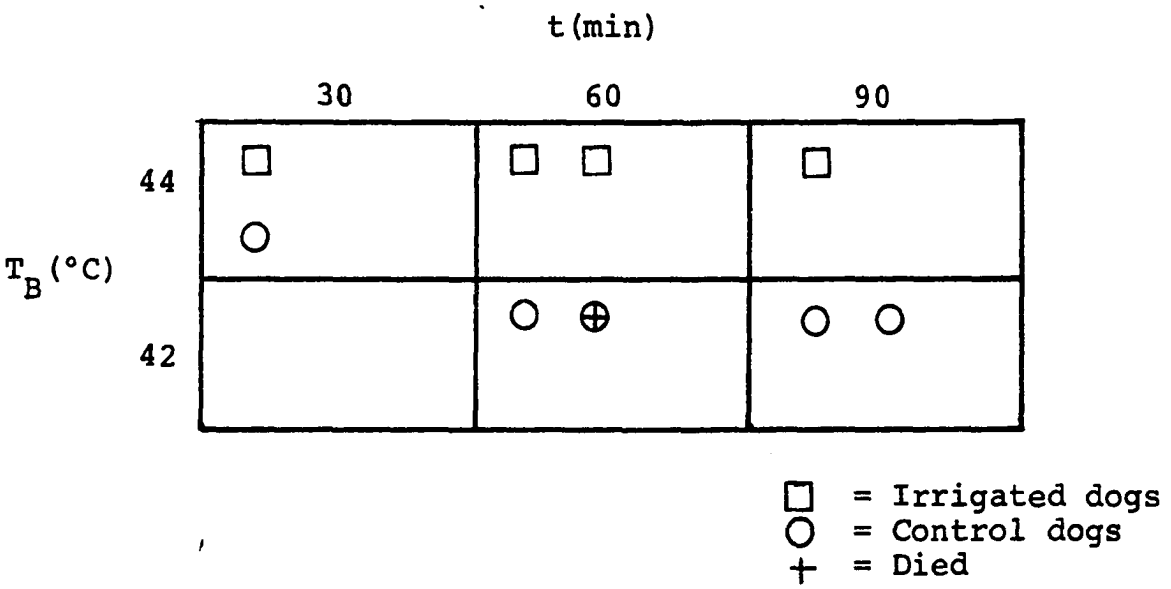


Table 4. Time-temperature matrix depicting survival response to hyperthermia with T_C held constant



Ranges in observed core temperatures at specific time intervals are compared with bath temperatures in Figures 3 and 4. At t = 0 a wide range is noted, especially at higher bath temperatures in both experimental and control groups. As time progressed to thirty minutes, the scatter of core temperatures became quite narrow. Figure 4 demonstrates the close grouping observed at forty minutes. If an average normalized graph of all the data (Figure 5) is observed, the time of forty to fifty minutes is required for the thermal values to approximate steady state conditions.

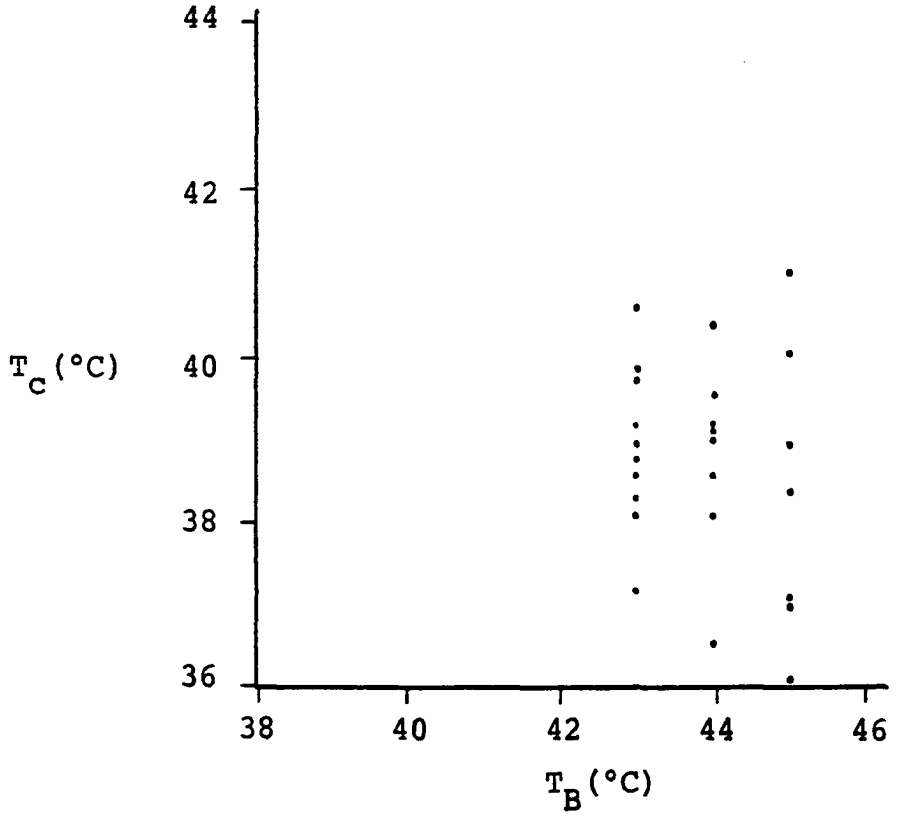
At each bath temperature, the core temperature data points of all irrigated dogs were plotted with respect to time (Figure 5). Data points from control dogs were plotted in a similar manner. Each population of points presented a time-based curve. A line was drawn through the population of data points which represented the average values. The technique utilized was similar to the method of least squares. The resulting curves were normalized by plotting a ratio of core temperature increase over initial bath temperature-core temperature differential against time. By this method, the values at different bath temperatures could be compared.

Depression of brain temperature below normal values (38.6°C) had previously been accomplished by nasal irrigation (52). Therefore, brain and core temperatures of seven irrigated and three control hyperthermic dogs were monitored to

Figure 3. Collated comparison of core temperature and bath temperature

t = 0.0 minutes

Irrigated



Control

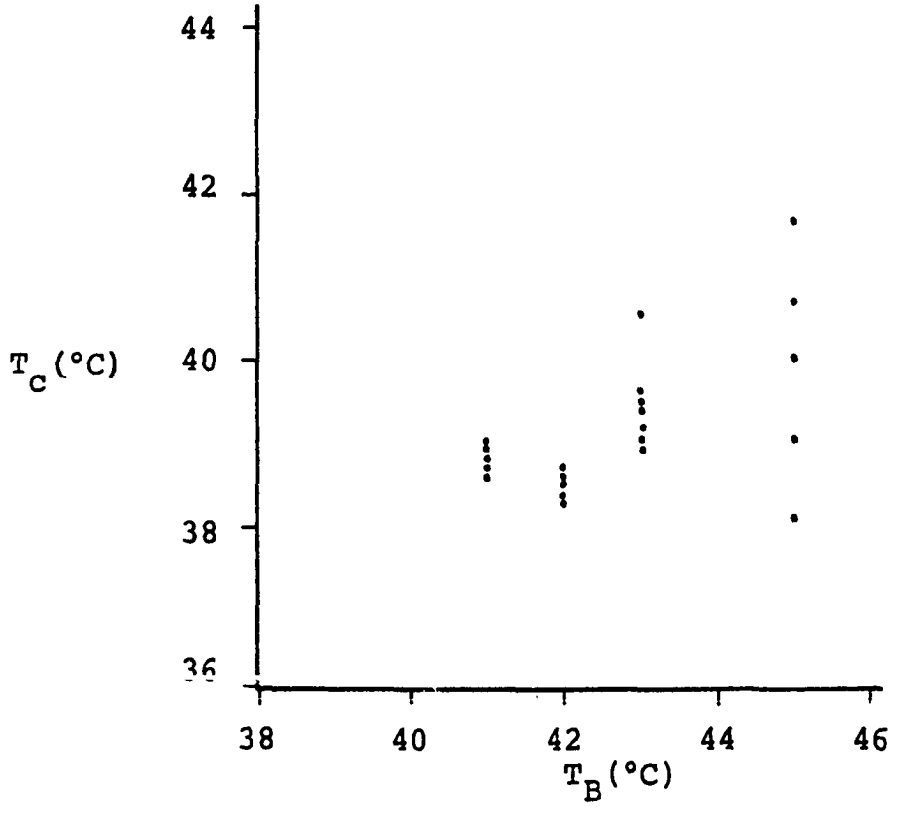
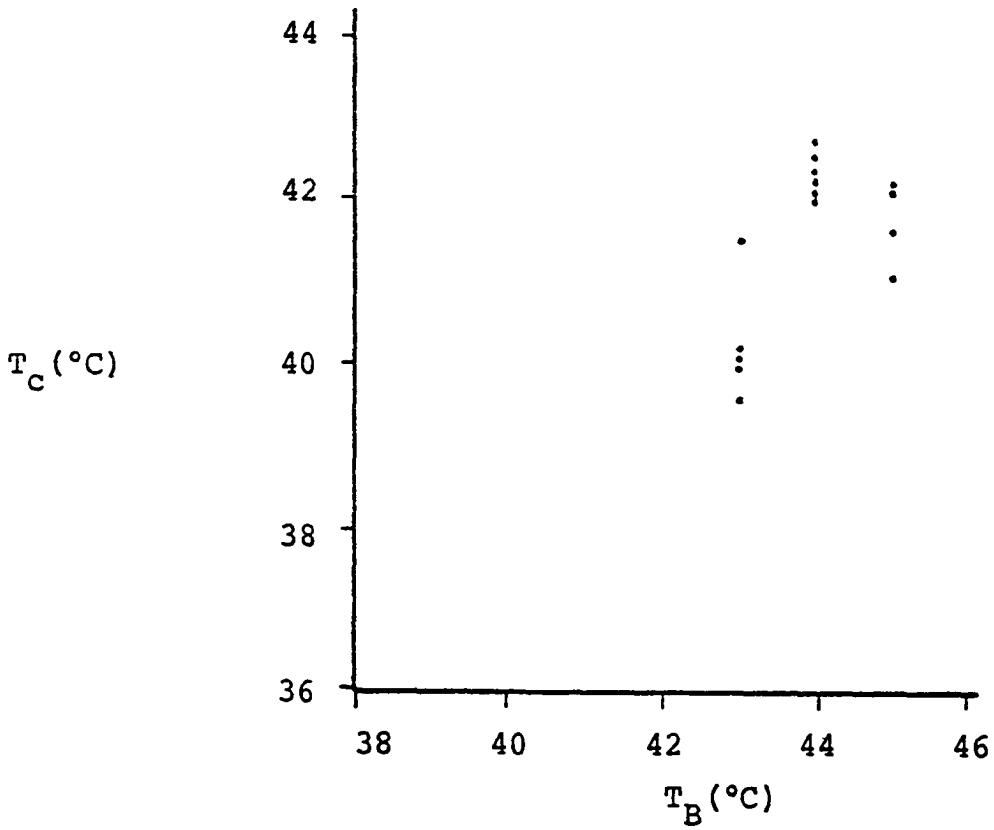


Figure 4. Collated comparison of core temperature and bath temperature

time = 40 min

Irrigated



Control

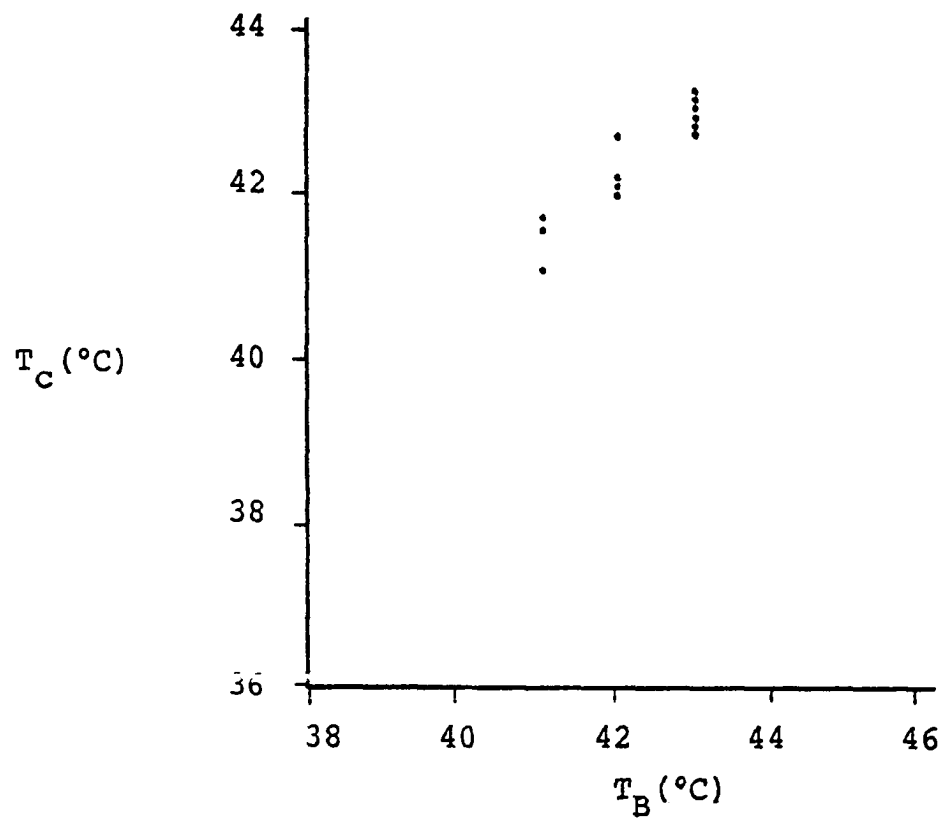
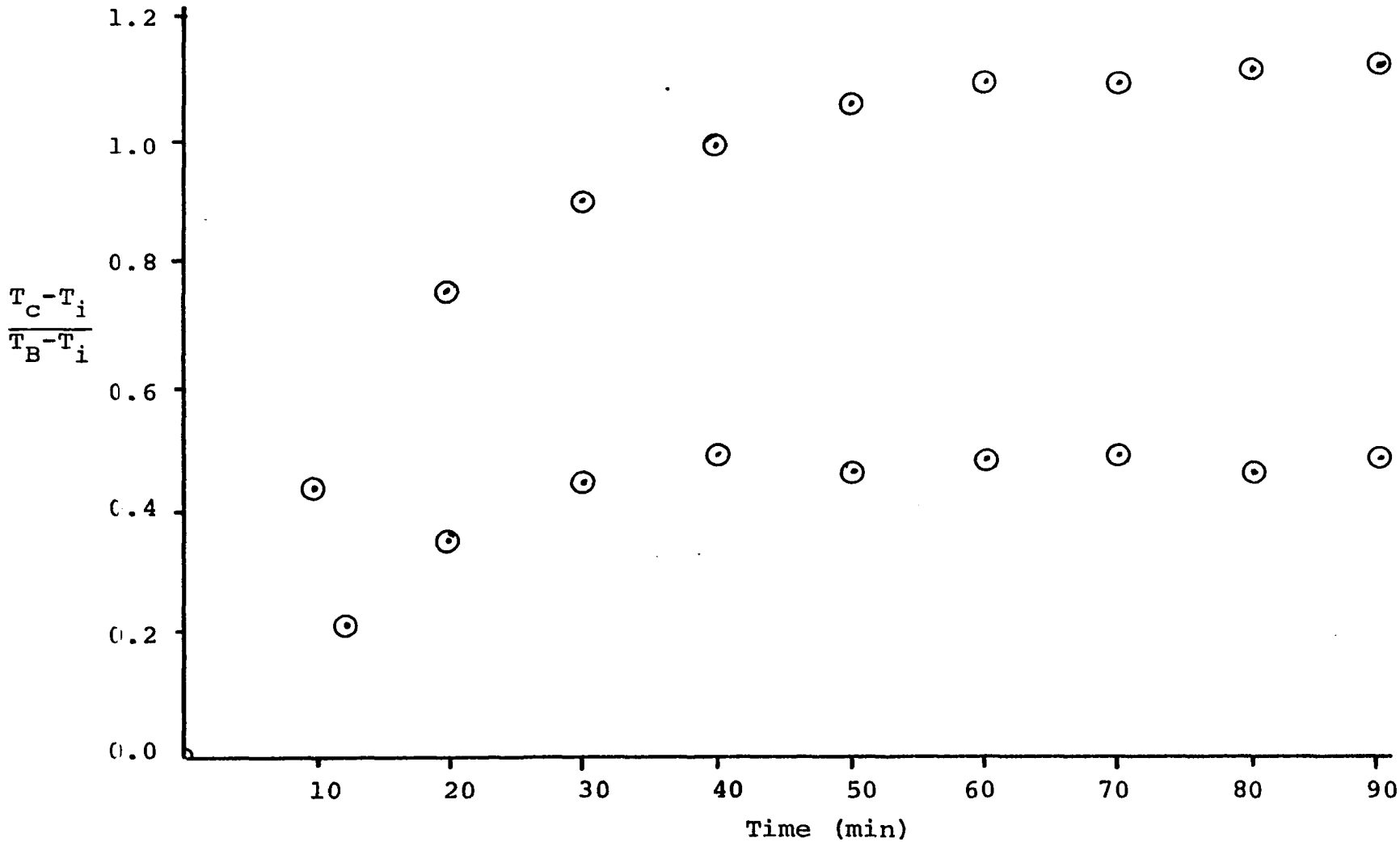


Figure 5. Normalized experimental data upper curve = control
lower curve = experimental


1.2
1.0
0.8
0.6
0.4
0.2
0.0
$\frac{T_c-T_i}{T_B-T_i}$
10
20
30
40
50
60
70
80
90
Time (min)

determine whether nasal irrigation could maintain a lower, safer temperature in the brain than the core temperature of these animals. It was shown that a differential between brain and core temperatures of 1° to 2°C could be maintained for the duration of the timed procedure.

Removal of the irrigating water resulted in an elevation of brain temperature to the existing hyperthermic core temperature. Replacement of the irrigator resulted in depression of brain temperature (Figure 6). Brain temperature corresponded to core temperature in the non-irrigated dogs.

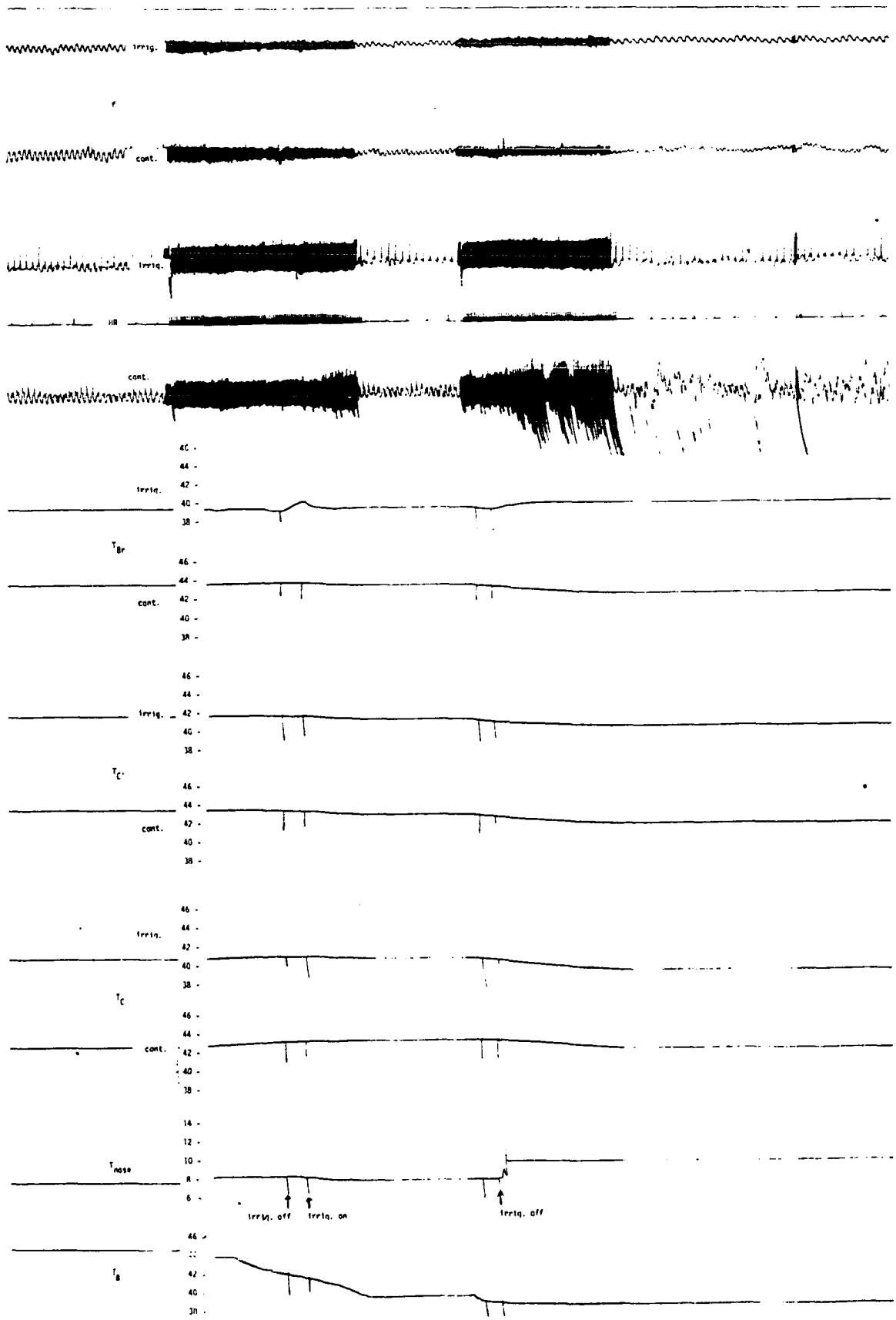
Recordings shown in Figure 6 were made at the terminus of the experiment, when water was being cooled. The control dog was dying, as is evidenced by the ECG tracing.

Core temperatures, as determined by stomach temperatures, rectal temperatures, and peritoneal temperatures, all agree consistently within 0.1°C, unless the animal was being heated or cooled. Stomach or rectal contents seemed responsible for a delay in response time for those sites.

Clinical Observations

Several clinical observations were made on both experimental and control animals which had core temperatures approaching 42.5°C. During the procedure, the anesthetic plane band width narrowed. The animals moved from one anesthetic stage to another very rapidly, due to the rapid metabolic rate

Figure 6. Photograph of recording depicting influence of nasal irrigation on T_{Br} independent of T_c


Irrig.
cont.
Irrig.
HR
cont.
Irrig.
T_{Br}
cont.
Irrig.
T_C
cont.
Irrig.
T_C
cont.
T_{nose}
Irrig. off
Irrig. on
Irrig. off
T_B

induced in the tissue cells. Panting was initiated when core temperatures reached 40°C to 42°C, but initiation of panting was more closely correlated with subcutaneous temperature. Non-irrigated animals began panting when the subcutaneous temperature reached 42°C. More spread was noted in the irrigated animals, which showed initiation of panting at subcutaneous temperatures of 41.5 to 43°C (Figure 7). Heart rate did not show any consistent relationship to either core or subcutaneous temperature. An increase in heart rate was noted with increased bath temperature, but no linearity between these parameters could be maintained.

Death during the procedure was uneventful. Respiratory rate diminished, while the amplitude was exaggerated. Ventricular tachycardia was noted; then, as heart rate slowed, the R-S segment increased in amplitude and duration. No other portions of the ECG tracing could be identified. All vital signs subsequently faded. This trend was reversed if animals were cooled rapidly when the abnormal respiratory and cardiac signs appeared.

After the procedure, the recovery period was prolonged. Often, animals were in a state of exhaustion for one to two hours. Once recovery developed, animals rapidly regained normal appetites, and no physical or neurological abnormalities were noted. If the animals did not become conscious within two hours after the procedure, death occurred within twelve hours.

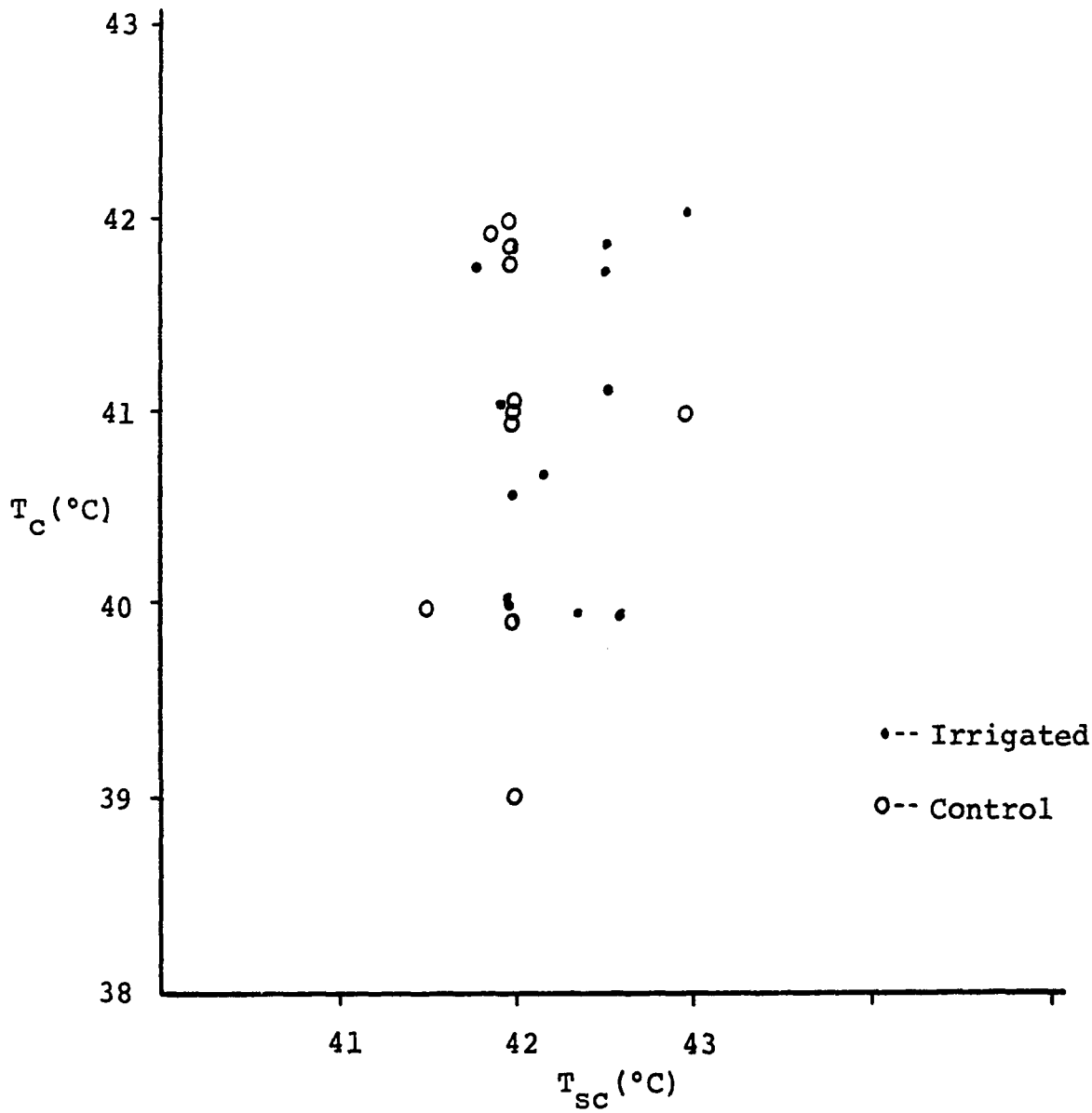


Figure 7. Temperatures observed at initiation of panting

These clinical signs are consistent with cited information referring to regenerative capacities of thermally sensitive organs. If hyperthermia follows van't Hoff's rule, metabolic rates of the animals with core temperatures of 42°C are 50 to 75% higher than in the normal state.

Examination of electrocardiographic and electroencephalographic data showed no observable alteration when terminal recordings were compared to initial recordings in either irrigated or surviving control dogs. Clinicopathological data showed no alteration when compared to the initial values in either irrigated or control dogs later than twenty-four hours after the experimental procedure.

Pathology

No remarkable lesions were evidenced in either the experimental or control animals which survived one week after treatment. Dog 115 suffered from chronic interstitial pneumonia that flared to an acute form. Dog number 152 suffered from chronic hepatitis. Both dogs were eliminated from the experiment.

Gross pathological changes observed in those animals which died acutely, revealed few petechia on the serosal surface of the stomach and intestine. Occasionally, the mesenteric lymph nodes were enlarged and edematous. In animals exposed to bath temperatures of 45° to 46°C, ecchymotic and suffusion hemorrhages were seen on the inside thigh, scrotum and inguinal

region. Microscopically, the gross lesions were supported, but no lesions were demonstrated in the central nervous system.

Pathology was apparently restricted mostly to the ultrastructural and biochemical level, because death was so rapid. This observation bears out cited information in the literature review.

Short Term Clinical Pathology

Blood gases demonstrated a shift to metabolic acidosis prior to the treatment after the animal was anesthetized. During the procedure, after the dog had been panting for a period of time, there consistently was a shift to respiratory alkalosis with partial compensatory metabolic acidosis. After the procedure, surviving animals reverted to slight metabolic acidosis, with partial compensatory respiratory alkalosis.

Dogs will develop slight dehydration during cage confinement. This, along with induction of anesthesia, is sufficient to render the animal in a mild state of metabolic acidosis. The second blood-gas sample was taken after the animal had been panting for a period of time, which accounts for the moderate state of respiratory alkalosis. Renal shut-down and reduction of the panting state reverted the animal back to a mild state of metabolic acidosis.

Although extreme hyperthermia would be expected to increase clotting time, no consistent pattern was noted. Urine volume

diminished markedly when the core temperature was maintained close to 42.5°C. This was more striking in non-irrigated than in irrigated dogs. Urine production volumes were not taken in animals prior to treatment, so quantitative comparisons with normal temperatures were not made. However, urine volume in the non-irrigated animals was much less than that of irrigated dogs in the same bath temperature. If core temperatures were held identical, urine volume did not differ.

Increases in protein and red blood cells were observed in the urine, but these were not marked. These were probably due to catheterization, and not to hyperthermia, as increases were seen in all animals, including those that did not receive sufficient heat to initiate panting.

Twenty-four hours after the treatment, animals that had achieved core temperatures in excess of 41.5°C had neutrophilia and lymphopenia. Occasionally, measured fibrinogen levels were elevated. The hemograms described no other abnormalities. Hemograms were similar to those seen in any stress syndrome of the canine.

Blood samples collected close to animal expiration revealed excessive hemolysis and cell dyscrasias, and no conclusions could be drawn other than that the blood cells were very fragile.

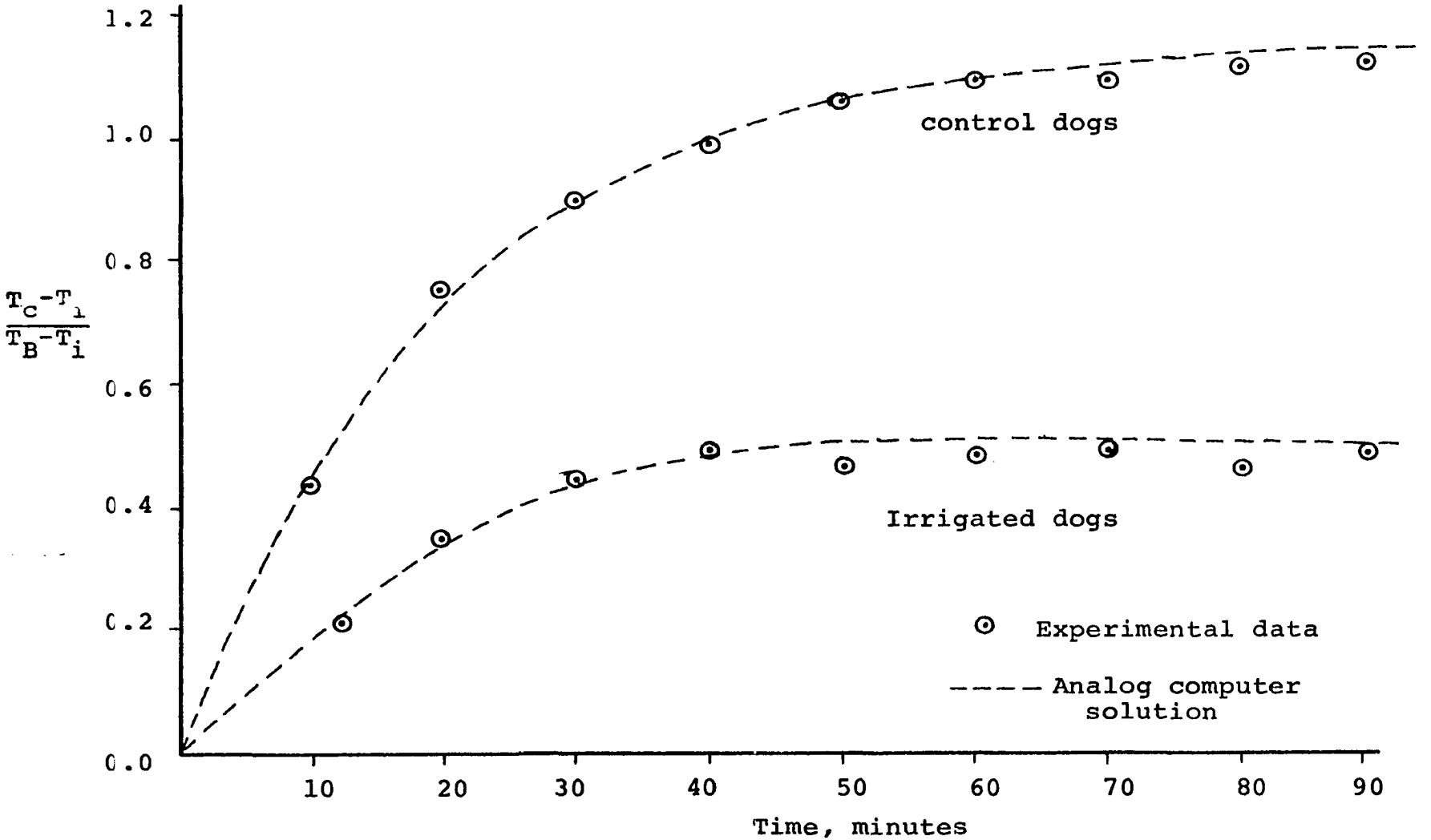
MATHEMATICAL MODEL

Bath temperature (T_B), duration of immersion (t), irrigation temperature (T_N) and irrigation flow rate are the controlling parameters or driving functions. In order to obtain predictable core temperature values the experimental design was presented to develop a family of curves at various temperature ranges and durations. These values were then normalized so they could be compared with each other (Figure 8). A mathematical model was thus developed utilizing a ratio of core temperature increase over initial bath temperature-core temperature differential, holding irrigation temperature and flow rate constant. Assuming metabolic rate is approximately linear with small temperature increases, the time required to achieve a desired core temperature can be determined by selecting an appropriate bath temperature.

Mathematical Solution

The first law of thermodynamics requires that energy be conserved. In the absence of work, the heat accumulation of a system equals heat input plus heat generated minus heat lost. The system here was defined as including the water bath, dog and cooled irrigating water. It was assumed that negligible heat was gained or lost with respect to the body in the air passageways. Although the head was not submerged, it was assumed that significant amounts of heat were not lost through its surface.

Figure 8. Comparison of experimental data with a mathematical model


1.2
1.0
0.8
0.6
0.4
0.2
0.0
$\frac{T_C - T_i}{T_B - T_i}$
control dogs
Irrigated dogs
Experimental data
Analog computer solution
10
20
30
40
50
60
70
80
90
Time, minutes

Furthermore, as experimental and control animals were treated identically, except for irrigation, these miscellaneous heat losses were assumed to be the same for both dogs.

Under these assumptions, the heat balance equation is:

$$mC_p \frac{dT_c}{dt} = UA(T_B - T_c) + \dot{M} - wC_p'\Delta T_w \qquad (1)$$

or, in words: heat accumulation equals heat from water bath plus heat from metabolism minus heat removed by irrigation, where:

m = mass of the experimental animal, Kgm

C_p = heat capacity of the animal, Kcal/Kgm °C

T_c = core temperature in °C

t = time, minutes

U = overall heat transfer coefficient, Kcal/m^2 min °C

A = surface area of the animal, M^2

T_B = bath temperature, °C

$\dot{M}$ = metabolic rate of the animal, Kcal/min

C_p' = heat capacity of water, Kcal/Kgm °C

w = rate of water flow, Kgm/min

ΔT_w = temperature change of the cooling water, °C.

Let $\theta = \frac{T_c - T_i}{T_B - T_i}$, where T_i is the initial core temperature.

Then, after rearrangement, (1) becomes:

$$\frac{d\theta}{dt} = \frac{UA}{mC_p}(1 - \theta) + \frac{\dot{M}}{mC_p(T_B - T_i)} - \frac{wC_p'\Delta T_w}{mC_p(T_B - T_i)} \qquad (2)$$

Now let $$a = \frac{UA}{mC_p}$$

and $$b = \frac{\dot{M}}{mC_p(T_B - T_i)}$$

and $$c = \frac{wC_p' \Delta T_w}{mC_p(T_B - T_i)}$$

then $\frac{d\theta}{dt} = a(1 - \theta) + b - c$, which can be solved to produce:

$$\theta = \frac{a + b - c}{a}(1 - e^{-at}) \qquad (3)$$

This fits the initial condition:

$$\theta(0) = \frac{a + b - c}{a}(1 - e^0) = \frac{a + b - c}{a}(1 - 1) = 0,$$

and can also be used to get the correct steady-state (long-time) result:

$$\theta(\infty) = \frac{a + b - c}{a}\left(1 - \frac{1}{e^\infty}\right) = \frac{a + b - c}{a}.$$

In the control dogs, where c = 0 (no irrigation), the data points at ninety minutes approached a value of:

$$\theta(\infty) = \frac{a + b}{a} = \frac{0.386 + 0.058}{0.386} = \frac{0.444}{0.386} = 1.150 \qquad (4)$$

where the values of a, b, (and c) are determined either by interpolating distances on Figure 8 or by the simulation of Equation 2 on an analog computer, as will be described below.

In the experimental dog, as can be seen in Figure 8,

$$\theta(\infty) = \frac{a + b - c}{a} = \frac{0.444 - 0.236}{0.386} = \frac{0.208}{0.386} = 0.540 \qquad (5)$$

These results agree very well with the collated experimental data, as shown in Figure 8. The dashed line through the experimental data points is the result of plotting the solution (Equation 3) using the parameters a, b and c as determined above.

Solution Utilizing the Analog Computer

Equation 2 was solved on an EAI Tr-48 analog computer, using

1 volt = 0.1 units of θ, $\theta' = 10\theta$

and 1 second = 10 minutes of real time, $T = \frac{t}{10}$

the equation becomes:

$$\frac{d\theta}{dT} = a'(10 - \theta') + b' - c' \qquad (6)$$

and when scaled (min^{-1})

$$\frac{d\theta}{dT} = \frac{10(UA)}{mC_p}(10 - \theta') + \frac{100\dot{M}}{mC_p\Delta T_i} - \frac{100wC_p'\Delta T_w}{mC_p\Delta T_i} \qquad (7)$$

The following results were obtained, directly from the computer, by fitting the data in Figure 8:

$$a' = \frac{10UA}{mC_p} = 0.386 \text{ min}^{-1},$$

$$\frac{1}{10} b' = \frac{1}{10}\left(\frac{100\dot{M}}{mC_p\Delta T_i}\right) = 0.058 \text{ min}^{-1},$$

and

$$\frac{1}{10} c' = \frac{1}{10}\left(\frac{100wC_p'\Delta T_w}{mC_p\Delta T_i}\right) = 0.236 \text{ min}^{-1} .$$

Comparison of Model with Experimental Data

The computer results for the coefficients a, b and c were then compared to the estimated values of the experimental parameters.

Water bath parameters

$$a' = \frac{10(UA)}{mC_p} = 0.386 \text{ min}^{-1} \qquad (8)$$

Substituting known values for the average dog (3),

$$UA = \frac{0.386}{\text{min}} \left(\frac{8\text{Kgm}}{10}\right)\left(\frac{0.86\text{Kcal}}{\text{Kgm°C}}\right)\left(\frac{60 \text{ min}}{\text{hr}}\right) = 16 \text{ Kcal/hr°C}, \qquad (9)$$

which is reasonable, since the dog's surface area (A) $\sim$ 0.5 to 0.7M^2, and the heat transfer coefficient (U) $\sim$ 20 to 25 Kcal/M^2 hr°C for this situation.

Metabolic parameters

$$b = \frac{10\dot{M}}{mC_p T_i} = \frac{0.058}{\text{min}} , \qquad (10)$$

or again substituting known parameters,

$$M = \frac{0.058\ mC_p \Delta T_i}{10}$$

$$= \left(\frac{0.058}{min}\right)\left(\frac{8Kgm}{10}\right)\left(\frac{0.86Kcal}{Kgm°C}\right)(5°C)\left(\frac{60\ min}{hr}\right) \qquad (11)$$

$$= 24(0.58)(0.86) = 12\ Kcal/hr.$$

For the average dog used in the experiment, the basal metabolic rate ($\dot{M}$) would be estimated at 16 Kcal/hr. The difference between the model value and the estimated value is most likely lost to the surroundings through the surface of the head and respiratory passages.

Irrigation cooling parameters

$$c' = \frac{10\ wC_p'\ \Delta T_w}{mC_p\ \Delta T_i} = 0.236$$

$$w\ T_w = \frac{(0.236)(8)(0.86)(4.0)}{(10)(1.0)} = 0.660\ Kgm°C/min$$

$$= 660\ ml°C/min,$$

or the equivalent of 480 ml/min of cooling water at a temperature change of 1.3°C, which compares with the observed values of 480 ml/min at about 0.5 to 1.0°C. The difference between the model and the measured values could be due in part to evaporative cooling on the irrigated nose.

A major conclusion which can be drawn from this analysis is that the mathematical model fits the experimental data

extremely well, in that it:

(1) gives the proper transient and steady-state results,

(2) describes the proper relative behavior between the experimental dogs and the control dogs, with only the term representing irrigative cooling (c) being added, and

(3) estimates proper and reasonable values for both the known and unknown experimental parameters.

CONCLUSIONS AND RECOMMENDATIONS

Extreme whole body hyperthermia was achieved by elevating core temperatures of dogs to 42°C, using a warm water bath. Irrigation of the alar fold of the nose with cold water (10 to 15°C) provided a means of elevating core temperature 0.5 to 1.5°C without lasting side effects. A brain-core temperature differential could be maintained by this technique for a long period of time (more than two hours). Maximum tolerable core temperature for the non-irrigated dog was 42°C for one to one and one-half hours, whereas that for the irrigated dog was in excess of 42.5°C. Time required for core temperature to reach steady-state was approximately forty minutes after correct bath temperature was achieved. Best results required a treatment duration of one to one and one-half hours. Panting was usually initiated at a subcutaneous temperature of 42°C. Dyspnea and ventricular tachycardia were observed when the animal approached death. These parameters, when monitored closely, revealed an "on-line" index with respect to viability. Death appeared to be due to heat exhaustion or hypovolemic shock.

An effective mathematical model of the system, that described the dynamic temperature changes, was developed. The analog solution matched the normalized experimental data points. The solution to the mathematical model also appeared to predict proper and reasonable values for known and unknown experimental

parameters.

Although available evidence indicates that maximum thermal tolerance levels are dictated by thermal denaturation of enzymes involved in cellular respiration, availability of metabolites may play an important role. Increases in metabolic rate required increases in glucose and oxygen utilization. If excessive quantities of glucose and oxygen were made available to the cells, the metabolic limitation might be reduced, thereby permitting greater elevation of core temperature (19).

Blood glucose determinations, oxygen consumption measurements, improved thermal monitoring, ultrastructural pathological studies, and automation of the physical system are major areas for further investigation. The present design was adequate to demonstrate that cerebral protection could be maintained under conditions of hyperthermia, and it was also adequate to permit a reasonable determination of the parameters required.

This technique provides a potential means by which to elevate the metabolic rate of cells to the point at which intracellular enzymes will be denatured and the cells destroyed. Cells with a high metabolic rate at normal body temperature should be the first to reach this limiting state during hyperthermia. Rapidly growing cancer cells have a very high metabolic rate, as do cells of cerebral tissue. Cerebral tissue can be thermally protected by a minimum of 0.5°C below

core temperature, as shown in this investigation. Therefore, core temperature can conceivably be elevated sufficiently to jeopardize the viability of cancer cells without cerebral damage.

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APPENDIX: SUMMARY OF EXPERIMENTAL DATA

Exp	Dog no.	wt (Kg)	N	t_B (min)	T_B (°C)	T_c (°C)	t_c (min)	f (min^{-1})	t_f (min)	Fate
1	101	5.5	+	60	45	42	50	30 min	180	E
1	111	5.5	-	60	45	43	30	160	30	D=run
2	114	7	+	60	45	42	30	200	30	E
2	104	7	-	60	45	41.5	20	144	10	D=run
3	106	6	+	30	45	39.0	20	27	30	E
3	113	6	-	30	45	42.0	30	180	30	D=run
4	107	5.5	+	30	44	Probe out		100	20	E
4	103	5.5	-	30	44	42.5	20	150	20	E
5	108	10	+	30	45	42.5	20	200	20	E
5	105	9	-	30	45	42	20	250	30	D=12 hr.
6	109	9	+	90	43	40.5	60	30	20	E
6	110	11	-	90	43	43	30	200	80	D=run
7	118	8	+	90	43	39	90	90	40	E
7	117	8	-	90	43	43	40	180	30	D=6 hr.
8	112	7	+	60	43	40.5	20	45	30	E
8	119	7	-	60	43	43	50	130	30	D=12 hr.
9	124	9	+	60	43	40.5	20	50	30	E
9	123	9	-	60	43	43	30	250	50	D=12 hr.
10	122	10	+	60	45	42	20	200	50	E
11	125	12	+	90	46	43	30	200	60	D=run
12	121	7	+	90	41	39	40	90	30	E
12	120	7	-	90	41	41	60	100	70	E
13	128	7	+	30	43	40.5	20	125	30	E
13	129	7	-	30	43	42	30	200	50	E
14	127	8	+	60	43	40.5	30	60	40	E
14	126	8	-	60	43	42.5	40	200	30	D=4 hr.

Exp	Dog no.	wt (Kg)	N	t_B (min)	T_B (°C)	T_C (°C)	t_C (min)	f (min^{-1})	t_f (min)	Fate
15	130	7	+	30	45	42.5	20	200	10	E
15	131	7	-	30	45	43	10	120	10	D=run
16	133	10	-	90	41	42	50	200	40	E
16	132	10	-	90	41	42	50	160	40	E
17	135	6	+	90	43	39	90	80	30	E
17	134	6	-	90	43	43.5	40	200	40	D=run
18	136	11	+	30	43	40.5	20	70	30	E
18	137	11	-	30	43	41.5	20	200	20	E
19	115	13	+	90	45	41	70	80	30	D=3 da
20	138	9	+	60	46	42.5	50	200	30	D=1 hr.
21	139	7	+	60	44.5	42	30	150	30	E
22	140	7	+	60	44	42	30	150	10	E
23	141	7	+	90	45	43	30	144	10	E
24	142	7	+	90	44.5	42	40	200	30	E
25	145	7	-	90	42	42	60	200	70	E
26	146	7	-	60	42.5	42.5	20	200	20	D=run
27	147	9	-	90	42	42	60	250	80	E
28	148	13	-	60	42	42	50	250	20	E
29	149	6	+	90	43	42	20	150	20	E
30	150	12	+	120	44	42.5	70	200	60	E
31	151	9	+	90	44.5	42.8	50	200	60	E
32	152	9	+	90	44	42.6	50	250	40	D=24 hr.
33	153	12	+	120	45	42.6	40	240	40	D